DOCKET NO: ISPH-0593 PATENT

REMARKS

Upon entry of this amendment, the claims pending are claims 1, 2, and 4-15. Claims 3 and 16-20 were previously cancelled. Any subject matter canceled from the claims by amendment is reserved for refiling in a continuation application filed during the pendency of this application. Applicants further affirm the correctness of the inventive entity in view of the cancellation of claims.

Claim 15 is amended to insert the words "*in vitro*" into the claim. Support for this amendment is found in the specification and particularly on pages 74-89. No new matter is introduced by this amendment.

A. Rejections Under 35 USC §112, first paragraph

Claims 15-20 are rejected under 35 USC §112, first paragraph, for lack of enablement. The examiner states that the specification does not reasonably provide enablement for the *in vivo*/whole animal application of antisense oligonucleotides targeted to SEQ ID NO: 3.

Without addressing the substance of this rejection and in an earnest attempt to advance prosecution, Applicants have amended Claim 15 to insert the phrase "*in vitro*" after "tissues" on line 3. In view of this amendment, Applicants respectfully request reconsideration and withdrawal of this rejection.

B. Rejections Under 35 USC §103(a)

Claims 1-2, and 4-14 stand rejected under 35 USC §103(a) as being unpatentable over the following combination of six documents: A. E. Sluder *et al*, 1997 *Devel. Biol.*, 184:303-319 ("Sluder"); H. Nishigori *et al*, 2001 *Proc. Natl. Acad. Sci., USA, 98*(2):575-580 ("Nishigori"); US Patent No. 5,801,154 ("Baracchini"); US Patent No. 5,998,148 ("Bennett");

H. M. Weintraub, **Jan. 1990** *Scient. Amer.*, pp.40- 46; and GenBank Accession No. L76571

The examiner states that

> "…even if the nhr-2 is not an equivalent of the instant heterodimer partner-1 of the instant rejection, it is clearly a member of the same class of receptors and Slunder [*sic*] *et al* have clearly shown the use of antisense for the study of function of a member of the same class of proteins, for example…..The Slunder [*sic*] reference as a whole, at least, provides a motivation to use antisense in the determination of gene function in nuclear hormone receptors and also shows success in doing so, for example." (OA pages 11-12)
>
> "At the very least the combination of references has taught that antisense has been successfully used to study nuclear hormone receptor function. . . and that one in the art should find antagonists of heterodimer protein-1 to find new insights into fetal growth and energy use. The art also teaches that antisense, in general, is applicable to the study of any gene and the art has provided clear guidance on how to make and use antisense to any target." (OA page 12).

Applicants respectfully request reconsideration and withdrawal of this rejection in view of the following remarks.

The combination of the above-cited six references fails to make a *prima facie* case of obviousness against the pending claims of this application.

A. The Cited Documents

Despite the examiner's contention, nhr-2 is not an "equivalent" of SHP-1. While it is true that nhr-2 is a member of the nuclear hormone receptor superfamily, it has been described by Sluder as defining "a *new subclass* of the superfamily". Nhr-2 is involved with early embryonic development. All that Sluder teaches is that

the injection of an unspecified antisense RNA into the syncytial region of the hermaphrodite gonad disrupts the function of nhr-2 in embryonic development.

In contrast, short heterodimer partner-1 (SHP-1) is a nuclear receptor subfamily 0 group B member. Human SHP-1 is described as ***an unusual member*** of the orphan receptor family (see specification page 2, lines 1-5), and is believed to be involved with obesity.

The fact that nhr-2 and SHP-1 are members of the nuclear receptor subfamily does **not** make obvious that a reference to nhr-2 can be taken to suggest anything about SHP-1. The nuclear hormone receptor *superfamily* is an *enormous* collection of receptors that share *some* structural and functional similarities, and many dissimilarities. Variations among the genes falling within that umbrella term are considerable, resulting in families, further divided into subfamilies, and further divided into groups, classes and subclasses. Sluder himself mentions a number of nuclear receptor superfamily subclasses, e.g., glucocorticoid receptor subclass, estrogen subclass, thyroid hormone class and retinoid receptor class.

In fact, when Applicants compared the Sluder sequence for nhr-2 (GenBank Accession No. NM_021969) with the GenBank Accession No. L76571 for human SHP-1 (SEQ ID NO: 3), they found no significant sequence homology at the gene or protein levels. Sluder even confirms the lack of similarity:

> "Second, outside the DNA binding domain, nhr-2 exhibits no significant similarity to known members of the NHR superfamily." (page 315, col. 2)

As it now stands, Applicants cannot find any basis upon which to conclude that nhr-2 has any meaningful equivalence to SHP-1 (SEQ ID NO: 3), regardless of their

common categorization into the nuclear receptor subfamily.

In view of the lack of equivalence between these genes, Applicants maintain that the examiner's characterization that Sluder teaches the use of an antisense sequence that disrupts expression of a gene equivalent to SHP-1, is incorrect. Sluder's teachings with respect to an unrelated gene to SHP-1 are simply not capable of suggesting anything, when combined with any other references to suggest the claims of the present invention.

Sluder contains no disclosure that suggests or refers to the SHP-1 gene or its encoded protein. Without any disclosure of SHP-1, Sluder cannot provide any suggestion that permits one to identify or suggest specific SHP-1 sequences as target sequences for binding by an antisense sequence. Sluder does not teach or suggest any sequence for antisense compounds that bind to SHP-1, as required by claim 1. Nor does Sluder suggest any methods for inhibiting SHP-1. Sluder does not teach or suggest a therapeutic utility of antisense compounds that bind SHP-1.

Nishigori refers to SHP as modulating the transcription activity of maturity-onset diabetes of the young (MODY) protein. Mutations resulting in the loss of expression of this gene were located in subjects with MODY. Nishigori concluded that genetic variation in the SHP gene contributed to increased body weight. Nishigori says nothing about antisense sequences and merely suggests in the conclusion of the paper that the activity of SHP could be regulated by "*yet-unidentified* ligands". See, page 479, col. 2.

The examiner suggests other quotations from Nishigori which further highlight the speculative nature

of the conclusions:

> "and the results described here **suggest** that such SHP agonists or antagonists **could have** a **significant** effect on body weight. . . accordingly, identification and characterization of **possible** ligands **should provide** new **insight** into mechanisms of fetal growth and energy expenditure."

With respect and with due regard to Nishigori, such paragraphs supply nothing to the combined art other than a **suggestion to try** new areas of research to obtain such "possible ligands", which then may be tested for the ability to impact the function of the SHP-1 gene. Nishigori does not teach or suggest antisense sequences to SHP-1.

Applicants acknowledge that the GenBank Accession number of an SHP-1 (SEQ ID NO: 3) indicates that SHP-1 was a known nucleic acid/amino acid molecule prior to the filing date. Further, the existence of SHP-1 sequences does not suggest antisense sequences or methods of using antisense sequences to SHP-1 or to any portion of SHP-1.

Weintraub is a review article relating to the field of antisense RNA or DNA, which was 11 years old at the time this application was filed. Bennett and Baracchini are cited for their generic teachings related to antisense compounds, although they specifically relate to proteins *unrelated* to SHP-1, namely microtubule-associated protein 4 (MAP4) and multidrug resistance-associated protein (MRP). These references are discussed for their generic teachings related to antisense compounds and not for any reference to SHP-1.

B. ***The combination of these six references does not make a prima facie case of obviousness with regard to the pending claims.***

Applicants respectfully submit that the combination of documents that disclose

(1) the sequence of SHP-1 (GenBank admission),
(2) a wish for "possible" ligands of SHP-1 that "should provide new insight into mechanisms of fetal growth and energy expenditure (i.e., Nishigori),
(3) documents cited to disclose generic antisense teachings (i.e., Weintraub, Bennett/Baracchini) and
(4) a document referring to a different protein, nhr-1 (Sluder)

do ***not*** provide a *prima facie* obviousness rejection of the above claims.

The rejection combines the generic teachings of Bennett, Baracchini and Weintraub with Nishigori's desire for ***possible*** ligands to SHP-1 (having a known sequence), and Sluder's use of antisense sequences to probe a different gene, the nhr-1. The documents (1) and (2) which relate to SHP-1 say absolutely nothing about antisense sequences. The documents cited in (3) and (4) discuss antisense sequence related to other proteins and provide some generic teachings about antisense technology.

None of these references, taken alone or together, teach or suggest a compound 8 to 50 nucleobases in length targeted to a nucleic acid molecule ***encoding human short heterodimer partner-1*** (SEQ ID NO: 3), which specifically ***hybridizes with and inhibits*** the expression of SHP-1, as required by the present claims. None teaches or suggests any sequence for antisense compounds that bind to SHP-1, as required by claim 1. Without such suggestion of the compounds, there can be no suggestion of any methods for using the sequences of claim 1.

The examiner states that "The art also teaches that antisense, in general, is applicable to the ***study*** of ***any*** gene...". With respect, this comment is unrelated to the present claims.

To make an obviousness rejection, the examiner may review the combined teachings of the cited prior art, knowledge of one of ordinary skill in the art, and the nature of the problem to be solved as a whole.[1] However, the courts have held that this range of sources does not diminish the requirement for actual evidence. Broad conclusory statements regarding the teaching of multiple references, standing alone, are not evidence.[2] Such a showing must be clear and particular.

With respect, no such clear and specific suggestion is made by the above combination that would make obvious the composition of claim 1 or the methods of use thereof stated in the other claims now pending. First, claim 1 and its dependent claims recite a ***specific*** gene, SHP-1. Taking each reference as a whole, this combination does not provide any *suggestion* of the antisense sequences that hybridize to and inhibit expression ***of SHP-1***.

Second, an obviousness rejection cannot be made by combining documents to make the bald suggestion that it is "obvious to try" to make antisense compounds to target *and inhibit expression of* SHP-1 simply because others

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1 Citing *In re Kotzab*, 217 F. 3d 1365, 1370, 55 USPQ2d 1313, 1317 (Fed. Cir. 2000)

2 See, e.g., *In re Dembiczak*, 50 USPQ2d 1614, 1616-1617 (Fed. Cir. 1999): "Our case law makes clear that the best defense against the subtle but powerful attraction of a hindsight-based obviousness analysis is rigorous application of the requirement for a showing of the teaching or motivation to combine prior art references. ... Combining prior art references without evidence of such a suggestion, teaching, or motivation simply takes the inventor's disclosure as a blueprint for piecing together the prior art to defeat patentability - the essence of hindsight. ..."; and In re Lee, 277 F.3d 1338, 1342-44, 61 USPQ2d 1430, 1433-34 (Fed. Cir. 2002).

have made antisense compounds to other proteins or used antisense technology to study other gene functions. The "obvious to try" standard is not the appropriate standard for a determination of patentability.

The combination of these references does not provide any *expectation of success* that if one did target the ***specifically claimed*** SHP-1 SEQ ID NO: 3 sequence of the present claims, that one would obtain antisense sequences with the desired *inhibitory* result. The only source of the required motivation to make and use antisense compounds directed to specific sequences of SHP-1 is provided by the Applicants' own specification. The only teachings that supply the necessary motivation and expectation of success that such a composition would be useful are provided by the instant specification. Obtaining the motivation for combination of the prior art cannot properly be provided by Applicants' own disclosure.

Applicants maintain that the combination of the cited prior art, when the teachings are taken *as a whole*, fails to supply both clear and specific suggestions and evidence which provide the motivation and a reasonable expectation of success required to set forth obviousness of the pending claims. Applicants' claims are directed to compounds that are neither taught nor suggested by these references in combination. Nor does such a combination provide any prediction of success with respect to SHP-1 as the target.

In view of the above amendments and these remarks, Applicants respectfully request that the examiner withdraw the outstanding rejections and permit the above pending claims to pass to issue in due course.

The Director is hereby authorized to charge any additional fees required with the filing of this paper or

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credit any overpayment in any fees to our deposit account number 08-3040.

Respectfully submitted,

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